The Role of Hemoglobin F in Avascular Necrosis among Sickle Cell Disease Patients: Implications for Clinical Management

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INTRODUCTION: Sickle cell disease, an inherited blood disorder affecting 70,000 to 100,000 individuals in the US, often leads to avascular necrosis (AVN) in around 30% of patients due to vaso-occlusive episodes. Notably, males show higher AVN susceptibility. This study investigates if HbF impacts AVN occurrence and if higher HbF quartiles are associated with delayed AVN diagnosis, offering insights for improved care. Examining HbF's influence on AVN occurrence and diagnosis age can inform clinical strategies (1, 2, 3, 4).

METHODS: This cross-sectional study uses medical records of 496 sickle cell disease (SCD) patients from Augusta, Georgia's Center for Blood Disorders. We examined AVN history, hemoglobin F (HbF), SCD-related complications, blood-thinning medication usage, lab values, hemoglobin electrophoresis, and COVID-19 history. Patients with AVN were categorized by HbF quartiles, to evaluate AVN risk among patients with different HbF quartiles using Logistic regression. ANOVA analysis was conducted to investigate the association of HbF quartiles with age at AVN diagnosis separately in males and females. This study aimed to assess the relationship between fetal hemoglobin (HbF) and the age of avascular necrosis (AVN) diagnosis by analyzing HbF quartiles in association with AVN diagnosis age

RESULTS: Females showed a significant reduction in AVN risk compared to males (OR = 0.6768, p = 0.035). However, the association between HbF quartiles and AVN risk was not statistically significant, with odds ratios close to unity (OR = 0.994, OR = 1.1581, OR = 1.4525). In Table 1, across all patients, HbF quartiles did not exhibit a significant association with AVN diagnosis age (p = 0.8068). However, sex-specific analysis revealed a significant correlation between HbF quartiles and mean AVN age in males (p = 0.02052), indicating earlier age of diagnosis of AVN among male patients with lower HbF quartiles. No such correlation was evident among females. (p=0.1454)

DISCUSSION: Our investigation into fetal hemoglobin (HbF) level and age of avascular necrosis (AVN) diagnosis age in sickle cell disease patients reveals compelling insights. The protective effect of female sex against AVN, reflected in a significant risk reduction (OR = 0.6768, p = 0.035), resonates with prior knowledge of sex based AVN differences. This enduring protection underscores the need to acknowledge sex-related variations in AVN pathogenesis and management. Moreover, our ANOVA analysis enriches our understanding of the relationship between HbF quartiles and AVN diagnosis age. Among males, higher HbF quartiles correlate with delayed AVN diagnosis (p = 0.02052), hinting at a potential protective role of elevated HbF levels. However, this pattern does not translate to females, revealing unique dynamics. This underscores the intricate interplay between HbF gender, possible role of estrogen as being protective against AVN and AVN development in sickle cell disease patients. Our study underscores the urgency of a nuanced perspective on AVN's development in sickle cell disease. HbF levels may influence AVN susceptibility and diagnosis age in males. A comprehensive understanding demands consideration of diverse genetic, vascular, and clinical elements. In future research, unraveling the protective mechanism of female sex against AVN and deciphering sex specific AVN risk factors remain pivotal. Exploring the intricate interaction between HbF, genetics, and clinical factors offers potential to deepen our grasp of AVN pathogenesis. Incorporating genetic polymorphisms, vaso-occlusive processes, and endothelial dysfunction can provide a holistic understanding of AVN's complexity.

To conclude, our study brings into focus the intricate interplay of HbF, sex, and AVN outcomes. While female sex consistently confers protection against AVN, the impact of HbF levels unveils intriguing sex-related variations. These findings advocate for a comprehensive assessment while shaping AVN risk evaluation and personalized interventions in the realm of sickle cell disease.

SIGNIFICANCE/CLINICAL RELEVANCE: Our findings reveal the complex relationship between fetal hemoglobin (HbF) and avascular necrosis (AVN) diagnosis age in sickle cell disease. By uncovering sex-specific associations and HbF quartile dynamics in males, this study opens avenues for personalized interventions and optimized AVN risk assessment strategies.

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Table 1: Assciation of HbF quantile with AVN diagnosis age

HbF quartile (all patients)	mean AVN age	p-value
Q1	36.6	0.8068
Q2	37.3	
Q3	35.2	
Q4	37.8	
HbF quartile (males)	mean_AVN_age	p-value
Q1	32.6	0.02052
Q2	34.9	
Q3	37.9	
Q4	41.7	
HbF quartile (females)	mean_AVN_age	p-value
Q1	41	0.1454
Q2	40.2	
Q3	31.6	
Q4	33.9	

Table 2: HbF Quantiles' Impact on Avascular Necrosis Risk, Controlling for Gender

Characteristic	OR[1]	95% CI[1]	p-value
Gender			
Male	—	—	
Female	0.6768	0.4705, 0.9713	0.035
HbF quartile			
Q1	—	—	
Q2	0.994	0.5938, 1.6637	0.982
Q3	1.1581	0.6920, 1.9415	0.576
Q4	1.4525	0.8762, 2.4187	0.149
[1] OR = Odds Ratio, CI = Confidence Interval			

Table 3: Association between HbF Quartiles and mean AVN Age, Controlling for Gender

HbF Quartile	Mean AVN Age	Linear Regression p-value	ANOVA p-value
Q1	36.6	0.958	0.8068
Q2	37.3		
Q3	35.2		
Q4	37.8		